KH

Day : Monday
Date: 2/26/2007

Time: 09:13:52

PALM INTRANET

Inventor Information for 10/642224

Inventor Name	City	State/Country
GOULIAEV, ALEX HAAHT	VEKSO SJ	DENMARK
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JOHANSEN, TINA HOLM	SMORUM	DENMARK
SCHEEL-KRUGER, JORGEN	GLOSTRUP	DENMARK
OLSEN, GUNNAR M.	FREDERIKSBERG	DENMARK
NIELSEN, ELSESBET OSTERGAARD	KOBENHAVEN K	DENMARK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity/Reexam | Foreign D

Search Another: Application# [ ] Search **or Patent#** [ ] Search

PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search

Attorney Docket # [ ] Search

Bar Code # [ ] Search

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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	154	544/13.ccls.	US-PGPUB; USPAT	OR	OFF	2007/02/26 08:40
L2	166	514/223.2.ccls.	US-PGPUB; USPAT	OR	OFF	2007/02/26 08:41
L3	285	l1 l2	US-PGPUB; USPAT	OR	OFF	2007/02/26 08:41

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L1      STRUCTURE UPLOADED

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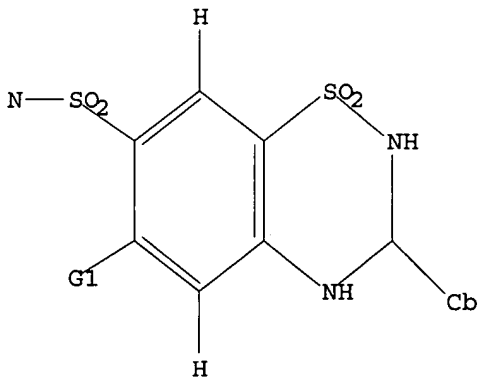


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G1 H,Ak

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -      128 TO ITERATE

100.0% PROCESSED      128 ITERATIONS                                  5 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
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PROJECTED ANSWERS:               5 TO      234

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SEARCH TIME: 00.00.01

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   172.10     172.31

FILE 'CAPLUS' ENTERED AT 08:25:37 ON 26 FEB 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 26 Feb 2007 VOL 146 ISS 10
FILE LAST UPDATED: 25 Feb 2007 (20070225/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

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L4 19 L3

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L4 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:850385 CAPLUS
DOCUMENT NUMBER: 145:293109
TITLE: Preparation of nitric oxide enhancing diuretic compounds, compositions and methods of use
INVENTOR(S): Garvey, David S.; Letts, L. Gordon; Earl, Richard A.; Ezawa, Maiko; Fang, Xinqin; Gaston, Ricky D.; Khanapure, Subhash P.; Lin, Chia-En; Ranatunge, Ramani R.; Stevenson, Cheri A.; Wey, Shiow-Jyi
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 91pp., which which which which
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

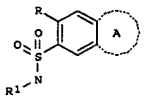
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006189603	A1	20060824	US 2006-360599	20060224
WO 2006091716	A2	20060831	WO 2006-US6375	20060224

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.:		
US 2005-655414P	P	20050224
US 2005-656545P	P	20050228
US 2005-685027P	P	20050526
US 2005-692228P	P	20050621
US 2005-749853P	P	20051213

OTHER SOURCE(S): MARPAT 145:293109
GI

L4 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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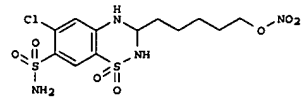
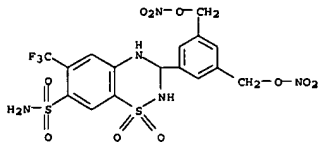


II

AB The invention describes novel compns. and kits comprising at least one nitric oxide enhancing diuretic compound I [R = Cl or CF3; R1 = H, alkyl, cycloalkyl, etc.; Ring A = substituted heterocycle], or pharmaceutically acceptable salts thereof, and, optionally, at least one nitric oxide enhancing compound and/or at least one therapeutic agent. Methods for preparing I are provided. Thus, e.g., II was prepared by cyclocondensation of 6-(nitrooxy)hexanal (preparation given) with 2-amino-6-chloro-1,3-benzenedisulfonamide. Assays for determining diuresis are described (data given). The invention also provides methods for (a) treating conditions resulting from excessive water and/or electrolyte retention; (b) treating cardiovascular diseases; (c) treating renovascular diseases; (d) treating diabetes; (e) treating diseases resulting from oxidative stress; (f) treating endothelial dysfunctions; (g) treating diseases caused by endothelial dysfunctions; (h) treating cirrhosis; (j) treating pre-eclampsia; (k) treating osteoporosis; (l) treating nephropathy; (m) treating peripheral vascular diseases; (n) treating portal hypertension; (o) treating central nervous system disorders; (p) treating metabolic syndrome; (q) treating sexual dysfunctions; and (r) hyperlipidemia. The nitric oxide enhancing diuretic compds. comprise at least one nitric oxide enhancing group linked to the diuretic compound through one or more sites such as carbon, oxygen and/or nitrogen via a bond or moiety that cannot be hydrolyzed.
IT 907624-13-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiadiazine nitric oxide derivs. as diuretics)
RN 907624-13-9 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-[3,5-bis[(nitrooxy)methyl]phenyl]-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide (9CI) (CA INDEX NAME)



own work

L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:549265 CAPLUS
DOCUMENT NUMBER: 131:184974
TITLE: Preparation of benzothiadiazines, quinazolines, and other aryl-fused heterocycles as positive AMPA-receptor modulators for treatment of memory and learning disorders
INVENTOR(S): Gouliaev, Alex Haahr; Larsen, Mogens; Varming, Thomas; Mathiesen, Claus; Johansen, Tina Holm; Scheel-Kruger, Jorgen; Olsen, Gunnar M.; Nielsen, Elsebet Ostergaard
PATENT ASSIGNEE(S): Neurosearch A/S, Den.
SOURCE: PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942456	A2	19990826	WO 1999-DK70	19990218
WO 9942456	A3	19991007		

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ZA 9609414	A	19970612	ZA 1996-9414	19961108
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AU 9925123	A	19990906	AU 1999-25123	19990218
AU 751384	B2	20020815		
ZA 9901301	A	19990913	ZA 1999-1301	19990218
TR 200002427	T2	20010122	TR 2000-200002427	19990218
EP 1071426	A2	20010131	EP 1999-904730	19990218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
HU 200101280	A2	20011028	HU 2001-1280	19990218
JP 2002504481	T	20020212	JP 2000-532408	19990218
EE 200000468	A	20020415	EE 2000-468	19990218
RU 2214405	C2	20031020	RU 2000-121882	19990218
NO 2000004121	A	20001017	NO 2000-4121	20000817
US 6943159	B1	20050913	US 2000-641814	20000818
US 2004043987	A1	20040304	US 2003-642224	20030818

PRIORITY APPLN. INFO.:		
DK 1998-226	A	19980218
WO 1999-DK70	W	19990218
US 2000-641814	A3	20000818

OTHER SOURCE(S): MARPAT 131:184974
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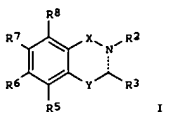
L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)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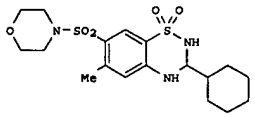
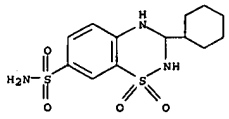

II

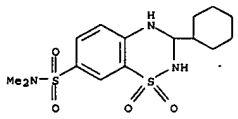
AB Benzothiadiazines, quinazolines, and other aryl-fused heterocycles (I) [wherein the bond represented by the broken line may be a single, double bond, or absent; and if the bond is absent, then the N is substituted with a H and R2; X = SO2, CO, or CH2; Y = -CH(R4)-, -N(R4)-, -N(R4)-CH2-, or O; R2, R4 = H, alkyl, cycloalkyl, aryl, benzyl, substituted carbonyl, or taken together with R3 = (un)substituted 4-7 membered ring; R3 = H, (un)substituted cycloalkyl, (un)substituted alkyl, (un)substituted alkoxy, acyl, or taken together with R2 or R4 = (un)substituted 4-7 membered ring, etc.; R5 = H, halogen, alkyl, alkenyl, alkynyl, aryl, or (un)substituted sulfonamido; R6, R7, R8 = H, halogen, (un)substituted alkyl, CN, cyanoalkyl, NO2, (un)substituted alkoxy, (un)substituted sulfonamido, (un)substituted aryl, etc.] were prepared as pos. AMPA-receptor modulators for treatment of memory and learning disorders. Thus, ClSO2NCO was added to a cooled solution of m-toluidine and nitroethane or nitromethane followed by addition of AlCl3 and reaction with H2SO4 to form a mixture of 2-amino-6-methylbenzenesulfonamide and 2-amino-4-methylbenzenesulfonamide. The latter isomer was separated by recrystn. and cyclized with cyclohexanecarbonyl chloride in a mixture of TEA, 4-(N,N-dimethylamino)pyridine, and THF to yield dihydro-3-cyclohexyl-6-methyl-1,2,4-benzothiadiazine-1,1-dioxide. The dihydrobenzothiadiazine-1,1-dioxide was chlorosulfonated with chlorosulfonic acid, sulfamoylated with morpholine, and reduced with DIBALH in toluene to give 3-cyclohexyl-6-methyl-7-morpholinosulfonyl-1,2,3,4-tetrahydro-1,2,4-benzothiadiazine-1,1-dioxide (II). Selected compds. of the invention were tested for in vitro inhibition of 3H-AMPA binding and exhibited IC50 values ranging from 3.4 μM to 45 μM. Two compds. were tested and showed significantly increased potentiation of AMPA-induced [3H]GABA release from cultured cortical neurons relative to the potentiation induced by 30 μM cyclothiazide. Expts. were performed in voltage clamp, and all tested compds. reversibly potentiated the current induced by application of 30 μM AMPA. The results of iontophoretic application showed that cyclothiazide did not exhibit any in vivo effects after i.v. administration but that five compds. of the invention enhanced AMPA evoked spike activity in an activity-dependent manner. Passive avoidance expts. were performed to test the pharmacol. effect of compds. on associative memory. Mean entry latency results for each group and the memory enhancing effect of different concns. of one compd. were given.

IT 240138-95-8P 240138-98-1P 240138-99-2P
240139-00-8P 240139-02-0P 240139-06-4P
240139-07-5P 240139-08-6P 240139-09-7P
240139-10-0P 240139-11-1P 240139-12-2P
240139-13-3P 240139-14-4P 240139-59-7P
240139-60-0P 240139-61-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiadiazines, quinazolines, and other aryl-fused heterocycles as pos. AMPA-receptor modulators for treatment of memory and learning disorders)

RN 240138-95-8 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-cyclohexyl-3,4-dihydro-, 1,1-dioxide (9CI) (CA INDEX NAME)



RN 240138-98-1 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-cyclohexyl-3,4-dihydro-N,N-dimethyl-, 1,1-dioxide (9CI) (CA INDEX NAME)



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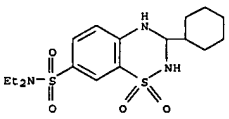
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-cyclohexyl-N,N-diethyl-3,4-dihydro-, 1,1-dioxide (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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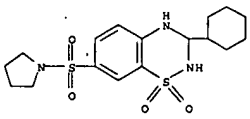

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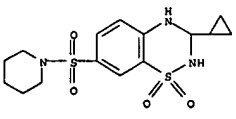

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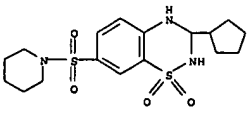

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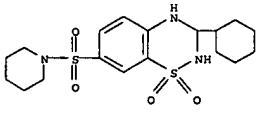
L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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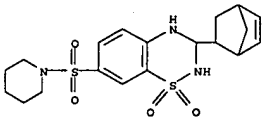

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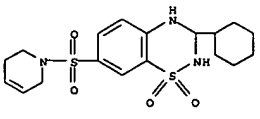
CN Pyridine, 1-[(3-cyclohexyl-3,4-dihydro-1,1-dioxido-2H-1,2,4-benzothiadiazin-7-yl)sulfonyl]-1,2,3,6-tetrahydro- (9CI) (CA INDEX NAME)



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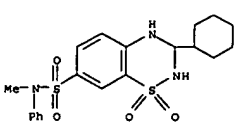

L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
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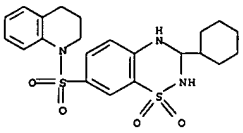

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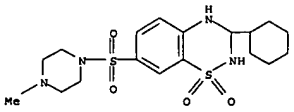

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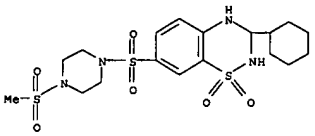
CN Piperazine, 1-[(3-cyclohexyl-3,4-dihydro-1,1-dioxido-2H-1,2,4-benzothiadiazin-7-yl)sulfonyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



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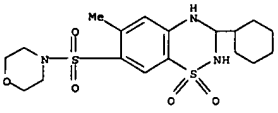
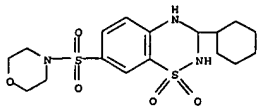
CN Morpholine, 4-[(3-cyclohexyl-3,4-dihydro-1,1-dioxido-2H-1,2,4-benzothiadiazin-7-yl)sulfonyl]- (9CI) (CA INDEX NAME)

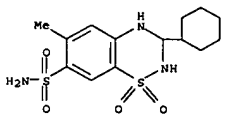
L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



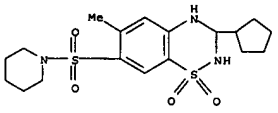
L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 240139-59-7 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-cyclohexyl-3,4-dihydro-6-methyl-, 1,1-dioxide (9CI) (CA INDEX NAME)



RN 240139-60-0 CAPLUS
CN Piperidine, 1-[(3-cyclopentyl-3,4-dihydro-6-methyl-1,1-dioxido-2H-1,2,4-benzothiadiazin-7-yl)sulfonyl]- (9CI) (CA INDEX NAME)



RN 240139-61-1 CAPLUS
CN Morpholine, 4-[(3-cyclohexyl-3,4-dihydro-6-methyl-1,1-dioxido-2H-1,2,4-benzothiadiazin-7-yl)sulfonyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1984:175285 CAPLUS
DOCUMENT NUMBER: 100:175285
TITLE: Substituted 4-phenoxy and 4-phenylthio prolines
INVENTOR(S): Haugwitz, Rudiger D.; Sprague, Peter W.
PATENT ASSIGNEE(S): E. R. Squibb and Sons, Inc., USA
SOURCE: Eur. Pat. Appl., 99 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

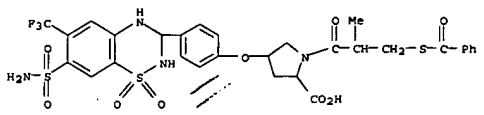
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 95584	A2	19831207	EP 1983-104221	19830429
EP 95584	A3	19840328		
EP 95584	B1	19870107		
R: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
ZA 8302762	A	19831228	ZA 1983-2762	19830419
CA 1258853	A1	19890829	CA 1983-426141	19830419
AU 8313837	A	19831103	AU 1983-13837	19830421
US 4681886	A	19870721	US 1983-488491	19830425
JP 58203987	A	19831128	JP 1983-76078	19830428
JP 04032071	B	19920528		
PRIORITY APPLN. INFO.:			US 1982-373570 A	19820430

OTHER SOURCE(S): CASREACT 100:175285; MARPAT 100:175285
GI

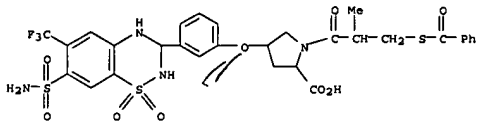
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [X = O, S; X1, X2 = CHNH, C:N; X3 = CO, SO2; R = H, alkyl, CH2Ph, CHPh2, cation; R1, R2 = H, halo, alkyl, alkoxy, haloalkyl, NO2, SO2NH2; R3 = H, alkyl, cycloalkylalkyl, (un)substituted phenylalkyl, haloalkyl, hydroxyalkyl; R4 = R5SCH2CHR6CO (R5 = H, acyl; R6 = H, alkyl, haloalkyl, Ph, CH2Ph, CH2CH2Ph, cycloalkyl), R8O2CCH2CH2NR7CO (R7 = alkyl, cycloalkyl; R8 = same as R), R9O2CCHR10NHCHR11CO [R9 = same as R; R10 = H, (CH2)mC6H4R12 (R12 = H, alkyl, alkoxy, halo, OH; m = 0-4), (un)substituted alkyl; R11 = H, (CH2)mR12, (un)substituted alkyl), R13P(O)(OR14)CH2CO [R13 = alkyl, (CH2)nR15 [R15 = C6H4R12, thienyl, furyl, pyridyl, cycloalkyl; n = 0-7]; R14 = H, alkyl, CH2Ph, CHPh2, ion, CHR17O2CR16 (R16 = H, alkyl, alkoxy, cycloalkyl, Ph, CH2Ph, CH2CH2Ph; R17 = H, alkyl, cycloalkyl, Ph)]] were prepared as antihypertensives (no data) due to their ability to inhibit angiotensin-converting enzyme. Thus, L-4-hydroxyproline was acylated with D-BzSCH2CHMeCOCl to give BzSCH2CHMeCO-Hyp-OH, which was esterified with MeOH/p-MeC6H4SO3H to give the Me ester, which was treated with m-HOC6H4CH(OMe)2 in the presence of Ph3P to give hydroxyproline II. The cyclocondensation of II with benzamide III gave quinazoline IV (R18 = Bz,

L4 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
R19 = Me), which was sapond. to give IV (R18 = R19 = H).
IT 89813-52-5P 89813-53-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 89813-52-5 CAPLUS
CN L-Proline, 4-[4-[7-(aminosulfonyl)-3,4-dihydro-1,1-dioxido-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazin-3-yl]phenoxy]-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-, (2α,4α)- (9CI) (CA INDEX NAME)



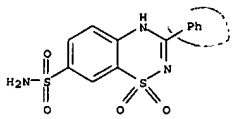
RN 89813-53-6 CAPLUS
CN L-Proline, 4-[3-[7-(aminosulfonyl)-3,4-dihydro-1,1-dioxido-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazin-3-yl]phenoxy]-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-, (2α,4α)- (9CI) (CA INDEX NAME)



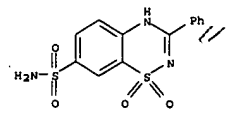
L4 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1973:72227 CAPLUS
DOCUMENT NUMBER: 78:72227
TITLE: 2H-1,2,4-Benzothiadiazine 1,1-dioxide derivatives
INVENTOR(S): Kresze, Guenter; Trede, Achim; Seyfried, Christoph
PATENT ASSIGNEE(S): Schering A.-G.
SOURCE: Ger., 5 pp.
CODEN: GWXXAW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 1470316	A	19690424	DE 1964-SC35190	19640521
DE 1470316	C3	19730628		
PRIORITY APPLN. INFO.:			DE 1964-SC35190	19640521

GI For diagram(s), see printed CA Issue.
AB R1SO2N:SO reacted with 4-R2C6H4N:CRNH2 in CHCl3 to give the 1-(sulfonylimino)-1,2,4-benzothiadiazines I. Thus, p-MeC6H4SO2N:SO was treated with PhC(:NPh)NH2 to give I (R = Ph, R1 = C6H4Me-p, R2 = H). Similarly, 9 more I (R = Ph, C6H4Cl-p, C6H4Me-p, OMe, Me; R1 = C6H4Me-p, Ph, Me; R2 = Cl, Br, H2NSO2) were prepared I were also oxidized to the S-oxides and S,S-dioxides.
IT 20043-38-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 20043-38-3 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-phenyl-, 1,1-dioxide (8CI, 9CI)
(CA INDEX NAME)



L4 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1968:496681 CAPLUS
DOCUMENT NUMBER: 69:96681
TITLE: Reactions with N-sulfinyl compounds. X. Benzothiadiazine derivatives from N-sulfinylsulfonamides and N-arylamidines
AUTHOR(S): Kresze, Guenter; Seyfried, Christoph; Trede, Achim
CORPORATE SOURCE: Tech. Hochsch. Muenchen, Munich, Fed. Rep. Ger.
SOURCE: Justus Liebigs Annalen der Chemie (1968), 715, 223-37
CODEN: JLACBF; ISSN: 0075-4617
DOCUMENT TYPE: Journal
LANGUAGE: German
OTHER SOURCE(S): CASREACT 69:96681
GI For diagram(s), see printed CA Issue.
AB Reaction of 4-RC6H4N:CR1NH2 with R2SO2N:SO (R = H, Cl, Br or SO2NH2, R1 = Ph or 4-ClC6H4, R2 = Me, Ph, or 4-MeC6H4) gave the corresponding I.
IT 20043-38-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 20043-38-3 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-phenyl-, 1,1-dioxide (8CI, 9CI)
(CA INDEX NAME)

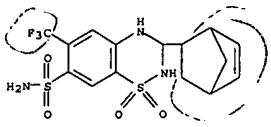


L4 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1967:10970 CAPLUS
DOCUMENT NUMBER: 66:10970
TITLE: 7-Sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide derivatives
INVENTOR(S): Mueller, Erich; Hasspacher, Klaus
PATENT ASSIGNEE(S): Boehringer Ingelheim G.m.b.H.
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3275625		19660927	US	19610123

GI For diagram(s), see printed CA Issue.
AB Novel derivs. of 7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, which are substituted in the 3-position by an alicyclic bicyclic radical, can be prepared by the following process. A mixture of 8.5 g. 6-chloro-4-aminobenzene-1,3-disulfonamide, 4 g. 2,5-endomethylene-Δ3-tetrahydrobenzaldehyde, and 25 cc. diethylene glycol dimethyl ether was heated 2 hrs. at 100° and the mixture allowed to stand 14 hrs. at room temperature to give 7.5 g. 3-(bicyclo[2,2,1]hept-2-en-6-yl)-6-chloro-7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (I), m. 229-30°. Similarly were prepared the following compds.: 3-(bicyclo[2.2.1]hept-6-yl)-6-chloro-7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m. 263-6°; 3-(2,3-dibromobicyclo[2.2.1]hept-6-yl)-6-chloro-7-sulfamoyl-3,4,dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m. 199-201°C. (decomposition): 3-(bicyclo[2.2.1]hept-2-en-6-yl)-6-trifluoromethyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m. 119°; 3-(bicyclo[2.2.1]hept-2-en-6-yl)-5-methyl-6-chloro-7-sulfamoyl-3-4,dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m 190-1°; 3-(bicyclo[2.2.1]hept-2-en-6-yl)-5,6-dichloro-7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m. 184°; 2-methyl-3-(bicyclo[2.2.1]hept-2-en-6-yl)-6-chloro-7-methylsulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m. 232-5°; 3-(bicyclo[2.2.2]oct-2-en-6-yl)-6-chloro-7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m. 276-7° (decomposition): 3-(5-methylbicyclo[2.2.1]hept-2-en-6-yl)-6-chloro-7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m. 197-9°; 3-(bicyclo[2.2.1]hept-2-en-6-yl)-6-chloro-7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide, m. 226-30°. Coated pills, suppositories, gelatin capsules, and liquid-containing ampuls are made from the various diuretic compds.
IT 859-24-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 859-24-5 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)

L4 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

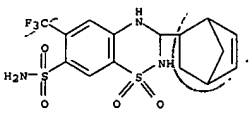


L4 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1965:498466 CAPLUS
DOCUMENT NUMBER: 63:98466
ORIGINAL REFERENCE NO.: 63:18126e-h,18127a
TITLE: 7-Sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides
INVENTOR(S): Thomae, Karl
PATENT ASSIGNEE(S): G.m.b.H.
SOURCE: 12 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

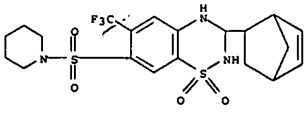
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
NL 296964		19650525	NL	
PRIORITY APPLN. INFO.:			DE	19620824

GI For diagram(s), see printed CA Issue.
AB The title compds. (I), useful as diuretics, are prepared Thus, to a solution of 16.28 g. 6-chloro-4-aminobenzene-1,3-disulfonyl chloride (II) in 50 ml. dry tetrahydrofuran (THF) is added dropwise at 20° under cooling 25 ml. of a solution containing 12.28 g. MeNH2 in 100 ml. THF. The mixture is diluted with 50 ml. acetone, filtered, and evaporated in vacuo at 20°. The oily residue is recrystd. twice from 260 ml. 1:1 MeOH-H2O at -10° to yield 3-methylsulfonamido-4-amino-6-chlorobenzenesulfonyl chloride (III), m. 146-8°. Similarly prepared are the following IV (R4, R5, R8, and m.p. given): Cl, H, H, 166-7° (V) (78.7% yield); CF3, H, H, 161-3° (VI); Cl, H, benzyl, 135-8° (CHCl3,) (VII) (62% yield). To a solution of 1.6 g. III and 15 mg. p-toluenesulfonic acid in dioxane is added at 70° 0.61 g. 2,5-endomethylene-1,2,5,6-tetrahydrobenzaldehyde (VIII); the mixture is held 20 min. at 70° and worked up to yield 2-methyl-3-(bicyclo [2.2.1] hept-2-en-6-yl)-6-chloro-7-chlorosulfonyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (IX), decomposed at 154-9° (MeOH-H2O). Similarly, V, VI, and VII are converted with VIII into the corresponding 3-(bicyclo [2.2.1] hept-2-en-6-yl) - 7- chlorosulfonyl-3,4-dihydro - 1,2,4 -benzothiadiazine 1,1-dioxides (R4, R5, R8, and m.p. given): Cl, H, H, 186-7° (MeOH-H2O) (X); CF3, H, H, -(XI); Cl, H, benzyl, 188-9° (decomposition) (XII). A solution of 1 g. IX in 25 ml. THF is treated 15 min. with gaseous NH3 to yield 2-methyl-3-(bicyclo[2.2.1]hept-2-en-6-yl)-6-chloro-7-sulfonamido-3,4-dihydro - 1,2,4 - benzothiadiazine 1,1-dioxide, m. 257-8° (EtOH-H2O). Similarly prepared are the 3-(bicyclo[2.2.1]hept-2-en-6-yl)-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides (I)(R1 : R2 : R3 : R5 : H) (R4, R6, R7, R8, and m.p. given): Cl, Me, H, Me, 231-3° (MeOH-H2O); Cl, Me, H, H (XIII), 212-14° (MeOH-H2O); Cl, H, H, H, 226-8° (MeOH-H2O); CF3, R6R7 : piperidino, H, 133-40° (decomposition); CF3, H, H, H, 165-8°; Cl, H, H, H, benzyl, 222-4° (decomposition). A solution of 0.808 g. XIII in dioxane is

L4 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
reduced with H and Raney Ni to yield 3-(bicyclo[2.2.1]hept-6-yl)-6-chloro-7- (N-methylsulfonamido)-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide, m. 246-8°.
IT 859-24-5P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-, 1,1-dioxide
4233-37-8P, Piperidine, 1-[[3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazin-7-yl]sulfonyl]-, S,S-dioxide
RL: PREP (Preparation)
(preparation of)
RN 859-24-5 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)



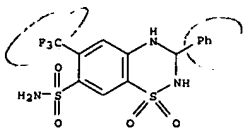
RN 4233-37-8 CAPLUS
CN Piperidine, 1-[[3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazin-7-yl]sulfonyl]-, S,S-dioxide (7CI, 8CI) (CA INDEX NAME)



L4 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1965:51748 CAPLUS
DOCUMENT NUMBER: 62:51748
ORIGINAL REFERENCE NO.: 62:9157e-g
TITLE: 1,2,4-Benzothiadiazine derivatives
INVENTOR(S): Novello, Frederick C.
PATENT ASSIGNEE(S): Merck & Co., Inc.
SOURCE: 2 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3160629		19641208	US 1961-101331	19610407
PRIORITY APPLN. INFO.:			US	19610407

GI For diagram(s), see printed CA Issue.
AB A process leading to the title compds. is described. Thus, 3.75 g. KMnO4 is added with stirring over 10 min. to a solution of 8.9 g. 6-chloro-7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide in 150 ml. H2O and 10 ml. 20% NaOH. The solution is stirred at room temperature 15 min. and warmed on a steam bath 5 min., EtOH added to destroy excess KMnO4, and the solution filtered and acidified to give 6- chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide (I), m. 337°. Similarly prepared is 6-methyl-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide, m. 345°.
IT 1170-25-8P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)
RN 1170-25-8 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide (6CI, 7CI, 8CI) (CA INDEX NAME)



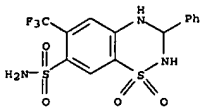
L4 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1965:51747 CAPLUS
DOCUMENT NUMBER: 62:51747
ORIGINAL REFERENCE NO.: 62:9157c-e
TITLE: Benzothiadiazine dioxides
INVENTOR(S): Cheney, Lee C.; Holdrege, Charles T.
PATENT ASSIGNEE(S): Bristol Laboratories International, S. A.
SOURCE: 18 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1368708		19640807	FR 1959-806279	19590929
US 3230218		19660118	US 1959-795595	19590226
PRIORITY APPLN. INFO.:			US	19580930

OTHER SOURCE(S): MARPAT 62:51747
GI For diagram(s), see printed CA Issue.
AB The title compds. (I) are used for the treatment of edemas associated with cardiac congestion, cirrhosis of the liver and kidney, and other diseases characterized by excessive accumulation of water. These compds. are obtained by the condensation of an aldehyde with a suitable aniline derivative Thus, to a solution of 0.09 mole 2-tri-fluoromethyl-4-amino-5-sulfamoylbenzenesulfonyl chloride in 125 cc. dioxane was added 15 cc. 40% CH2O, the solution added to 125 cc. concentrated NH4OH, NH4OH distilled after 1.5 hrs., and the residue refluxed 2.5 hrs. to give I (R = R1 = H), m. 260-4°. The following I were similarly prepared (R, R1, and m.p. given): Me, Me, 216-21°; H, Et, 256-8° (decomposition) and 262-3° (decomposition) (2 forms); H, Me, 247-50° (decomposition); H, PhCH2, 221-3°; H, 2-pyridyl, 310-11°; H, Cl3C, 283-5° (decomposition); H, Ph, 219-21°. By using cyclohexanone ethylene acetal, 7-sulfamoyl-6-trifluoromethylspiro [2H-1,2,4-benzothiadiazine-3,1'-cyclohexane] 1,1-dioxide, m. 260-2°, was obtained.
IT 1170-25-8P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)
RN 1170-25-8 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide (6CI, 7CI, 8CI) (CA INDEX NAME)

L4 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

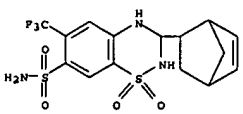


L4 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1963:462475 CAPLUS
DOCUMENT NUMBER: 59:62475
ORIGINAL REFERENCE NO.: 59:11536h,11537a-b
TITLE: Dihydrohenzothiadiazine dioxides
PATENT ASSIGNEE(S): Eli Lilly & Co.
SOURCE: 4 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 915236		19630109	GB	
PRIORITY APPLN. INFO.:			US	19601031

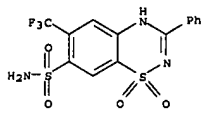
GI For diagram(s), see printed CA Issue.
AB The preparation of 3-(bicyclo[2.2.1]hept-2-en-5-yl)-7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides (I) is described. These compds. are used as diuretic agents. 5-Chloro-2,4-disulfamoylaniline (28.5 g.) was suspended in 195 ml. 95% aqueous EtOH and 150 ml. 6N aqueous HCl, and 12.2 g. bicyclo[2.2.1]hept-2-en-5-ylcarboxaldehyde added, and the reaction stirred to effect solution of the aldehyde. The mixture was kept at room temperature 12 hrs. and the precipitate of I (R = Cl) filtered off and washed to remove HCl, m. 230-1° (EtOAc). Similarly prepared was I(R = CF3), m. 221°. These compds. were also prepared by cyclizing bicyclo[2.2.1]hept-2-en-5-ylcarboxaldehyde with 1,3-disulfamoyl-4-fluoro-6-chloro(or 6-trifluoromethyl)benzene in the presence of NH8 or by acylating 1,3-disulfamoyl-4-amino-6-chloro- (or trifluoromethyl)benzene with an anhydride or acid halide of bicyclo[2.2.1]hept-2-enyl-5-carboxylic acid, cyclizing the acylated product produced with an alkali, and then reducing the benzothiadiazine cyclization product to form a dihydrobenzothiadiazine.
IT 859-24-5P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)
RN 859-24-5 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)



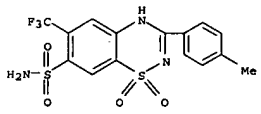
L4 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L4 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1963:53284 CAPLUS
DOCUMENT NUMBER: 58:53284
ORIGINAL REFERENCE NO.: 58:9078c-h
TITLE: Synthesis of 1,2,4-benzothiadiazine 1,1-dioxide derivatives
AUTHOR(S): Klosa, Josef
CORPORATE SOURCE: Privatlab., Berlin
SOURCE: Journal fuer Praktische Chemie (Leipzig) (1962), 18, 313-20
CODEN: JPCEAO; ISSN: 0021-8383
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 58:53284
GI For diagram(s), see printed CA Issue.
AB The acylation of 5-trifluoromethylaniline-2,4-disulfonamides with carboxylic acids in the presence of POCl3 and subsequent cyclization of the resulting acylanilide analogs with concentrated H2SO4 yielded a series of 3-substituted 6-trifluoro-7-aminosulfonyl-1,2,4-benzothiadiazine 1,1-dioxides. 5,2,4-CF3(H2NO2S)C6H2NH2 (I) (6.4 g.), 2 cc. AcOH, and 6 cc. POCl3 heated 10-15 min. with stirring at 60-70° and then to 90-110°, cooled, diluted with 50 cc. H2O, boiled, cooled, and filtered yielded 6.7 g. N-Ac derivative (II) of I, leaflets, m. 292-4° (80% iso-PrOH) with browning from 250°. I (6.4 g.) in 30 cc. MePh and 2 cc. AcOH refluxed, treated during 15 min. dropwise with 6 cc. POCl3, refluxed 1 hr., cooled, and filtered, and the residue treated with 30 cc. H2O, heated on the water bath, and worked up in the usual manner yielded 6.8 g. II. Similarly were prepared the following III (R and m.p. given): EtCO, 312-14° (80% iso-PrOH); PrCO, 295-7° (needles); iso-PrCO, 282-4° (60% iso-PrOH); iso-BuCO, 208-10° (gray crystal powder); C7H15CO, 158-60° ClCH2CO, 298-300° (with browning from 250°); Cl2CHCO, 208-10° [resolidified at 220° and remelted at 296-8° (decomposition)]; CCl3CO, 228-30° [resolidified at 234° and remelted at 293-5° (decomposition)] CH2BrCO, 228-30° (resolidified at 250°); CHBr2CO, 220-2° (with browning at 210° (decomposition); MeCHBrCO, 304-6° with sintering an turning brown-yellow from 250°; Me2CHCHBr, 128-30° (needles); Bz, 250-2° (resolidified at 270° and decompose at 328-30°]; p-MeOC6H4CO, m. 246-8° (resolidified at 260° and decomposed up to 290°); 3,4,5-(MeO)3C6H2CO, 212-14°; p-MeC6H4CO, 165-7° with browning from 250° (needles); PhCH2CO, 124-6° (80%, iso-PrOH); Ph2CHCO, 228-30° (needles); EtPhCHCO, 162-4° (crystal powder); picolinoyl, 158-60° (crystal powder); nicotinoyl, 226-8° (needles); isonicotinoyl, 233-5° (needles). II (6 g.) added in portions with stirring to 20-30 cc. concentrated H2SO4, heated 2-3 hrs. at 60-70°, kept overnight, added slowly with stirring into 50 cc. H2O and filtered after 2 hrs. gave 5.2 g. (crude) 3-methyl-6-trifluo omethyl-7-aminosulfonyl-1,2,4-benzothiadiazine 1,1-dioxide(IIIa), m. 334-6° (iso-PrOH). IIIa(1 g.) in 40 cc. Ac2O refluxed 5 hrs., filtered hot, and cooled gave 1.1 g. N-Ac derivative (IV) of IIIa, m. 298-300° (80% iso-PrOH) (decomposition). Similarly were prepared the

L4 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
following IVa (R and m.p. given): Et (V), 346-8° (decompn.); Pr, 318-20°; iso-Pr, 296-8° iso-Bu, 235-7°; C7H15, 203-5°; ClCH2, 312-14°; Cl2CH, 306-8°; CCl3, 293-5°; BrCH2, 292-4°; Br2CH, 258-60° MeCHBr, 306-8° (decompn.); Me2CHCHBr, 160-2°; Ph, 330-2°; p-MeOC6H4, 290-2°; 3,4,5-(MeO)3C6H2, 228-30° (iso-PrOH); p-MeC6H4, 280-2°; PhCH2, 164-6° (80% iso-PrOH); Ph2CH, 258-60° (iso-PrOH); EtPhCH, 237-9°; 2-pyridyl, 302-4°; 3-pyridyl, 334-6°; 4-pyridyl, 316-18°. IV (1 g.) refluxed 20 min. in 200 cc. H2O, filtered hot, and cooled gave 0.6 g. IIIa, needles, m. 332-4° (80% iso-PrOH). V with Ac2O gave in the usual manner the Ac deriv., m. 296-8°, which was hydrolyzed with H2O to V, needles, m. 346-8°. IIIa (1 g.) and 30 cc. (EtCO)2O refluxed 6 hrs. yielded 0.9 g. EtCO deriv. (VI) of IIIa, m. 284-6° (decompn.) (80% iso-PrOH); V with (EtCO)2O gave similarly the EtCO deriv. (VII) of IIIa, m. 280-2° (60% iso-PrOH). VI and VII refluxed with dil. H2SO4 yielded IIIa. and V, resp.
IT 746-82-7P, 4H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide 859-25-6P, 4H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-p-tolyl-6-(trifluoromethyl)-, 1,1-dioxide 1550-90-9P, 4H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-(p-methoxyphenyl)-6-(trifluoromethyl)-, 1,1-dioxide 1691-04-9P, 4H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)
RN 746-82-7 CAPLUS
CN 4H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)

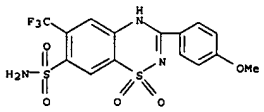


RN 859-25-6 CAPLUS
CN 4H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-p-tolyl-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)

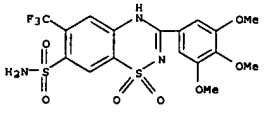


L4 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RN 1550-90-9 CAPLUS
CN 4H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-(p-methoxyphenyl)-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)

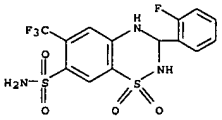


RN 1691-04-9 CAPLUS
CN 4H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)



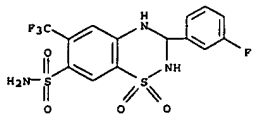
L4 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1963:33410 CAPLUS
DOCUMENT NUMBER: 58:33410
ORIGINAL REFERENCE NO.: 58:5689c-h,5690a
TITLE: A simple synthesis of dihydrobenzothiadiazine dioxide derivatives
AUTHOR(S): Klosa, Josef; Voigt, Hans
CORPORATE SOURCE: Privates Forschungslabor, Berlin-Zehlendorf
SOURCE: Journal fuer Praktische Chemie (Leipzig) (1962), 16, 264-76
CODEN: JPCEAO; ISSN: 0021-8383
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 58:33410
AB 6-Chloro- (I) and 6-trifluoromethyl-7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (II) derivs., substituted at C-3 with R which was H, alkyl, aryl, or aralkyl, were synthesized by heating 2,4-disulfamoyl-5-chloroaniline (III) or the 5-trifluoromethyl analog (IV), resp., with RCHO (V) in aqueous HCl (EtOH added when III or IV were insol. in water). Nonaq. media were not necessary for the reaction. V which either reacted or did not react with III and IV were tabulated. Two mechanisms were discussed for the condensation reaction in aqueous media and one in nonaq. media. III (5.7 g.) was suspended in 150 ml. H2O, 0.02 mole V and 3 ml. concentrated HCl added, and if H2O-soluble addnl. 50 ml. H2O added, otherwise 50 ml. EtOH added, refluxed 40-60 min., and crystalline I filtered off hot. II were similarly prepared from IV. Acetals of halogenated V also condensed with III and IV to yield I and II, resp. Thus, 30 g. III was suspended in 80 ml. H2O and 50 ml. concentrated HCl, a solution of 18 ml. of the acetal of BrCH2CHO in 110 ml. EtOH added, the mixture refluxed 4 hrs., cooled, and the product filtered off and washed with H2O to yield 38 g. I (R = BrCH2) (VI), m. 224-6°. Similarly the acetals of Cl2CHCHO and ClCH2CHO yielded the corresponding I and II. I and II where R = 5-nitro-2-furyl were preferably prepared from 5-nitrofurfural diacetate. The following I and II were prepared by the above routes (R and m.p. of I and II given): H, --, 261-3°; Me, 254-6°, 246-8°; Et, 266-8°, 262-4°; Pr, 255-7°, 228-30°; iso-Pr, 290-2°, 248-50°; Bu, 190-2°, 210-12°; iso-Bu, 244-6°, --; CH2Cl, 234-6°, 237-9°; CHCl2, 242-4°, 244-6°; CCl3, 300-2°, --; CH2Br, 224-6°, 206-8°; CH2I (VII), 198-200°, 194-6°; PhCH2, 246-8°, 220-2°; PhCHMe, 220-4° (when recrystd. from EtOH yielded a soluble form, m. 226-8° and a slightly soluble form, m. 238-48°), 235-7°; PhCH:CH, 248-50°, 171-3°; 4-pyridyl, 326-8°, --; 2-furyl, 212-14°, 252-4°; 5-nitro-2-furyl, 220-2°, 212-14°; p-ClC6H4, 236-8°, 224-6°; p-O2NC6H4, 242-4°, 235-7°; p-ClC6H4CH2, 238-40°, 240-42°; p-MeOC6H4CH2, 224-6°, 245-7°; p-MeC6H4CH2, 230-2°, --; o-FC6H4, 245-7°, 243-5°; m-FC6H4, 223-5°, 248-50°; antipyryl, 244-6°, oil. VI (20 g.) and 16 g. KI in 200 ml. anhydrous Me2CO refluxed 5 hrs., half the solvent evaporated, and H2O added; 22 g. VII separated

L4 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
When, however, the reaction was carried out in H2O or EtOH only decompn. products were obtained. A suspension of 60 g. III, 2.6 l. H2O, 20 ml. concd. HCl, and 18 ml. 38% aq. HCHO (VIII) was stirred and refluxed 20-30 min. when all dissolved, the mixt. was refluxed 30 min., C added, and the mixt. filtered hot. From the filtrate sepd. on cooling 53 g. cryst. I (R = H) (IX), m. 270-2° (H2O). IX in hot 0.1N NaOH hydrolyzed to III. Excess VIII in the above reaction caused polymer formation. Thus, when a suspension of 5.7 g. III in 50 ml. H2O contg. 4 ml. 37% aq. VIII, 2 ml. concd. HCl, and 100 ml. EtOH was refluxed 1 hr., cooled, and 50 ml. H2O added 6 g. colorless resin (X), m. 265-70°, sepd., sol. in alcohols and other org. solvents. Polymer formation was avoided by carrying out the reaction in aq. NH3. Thus, a mixt. of 6.8 g. III, 40 ml. concd. aq. NH3, and 0.7-1 g. VIII (as the 37% aq. soln.) (or a large excess of VIII may also be employed) stirred and refluxed 20-30 min., decolorized with C,
and filtered hot gave 4.5 g. IX, m. 270-2°. IX in 95% yield was also obtained after 1 hr. reflux of 57 g. III, 2.5 l. H2O, 20 ml. 25% NH3,
and 30 ml. 37% aq. VIII. Mixed m.ps. of X with III or IX showed no depression, indicating that the wide range of m.ps. of IX reported (from III and gaseous HCl in nonaq. media) (Freeman and Wagner, CA 46, 1559i) was due to the presence of impurities in IX. The diuretic effects of I and II were tabulated and discussed.
IT 748-17-4P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-(o-fluorophenyl)-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide
748-18-5P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-(m-fluorophenyl)-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide
748-19-6P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-(p-chlorophenyl)-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide
3872-12-6P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(p-nitrophenyl)-6-(trifluoromethyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)
RN 748-17-4 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-(o-fluorophenyl)-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide (8CI) (CA INDEX NAME)

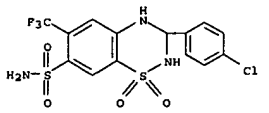


RN 748-18-5 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-(m-fluorophenyl)-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)

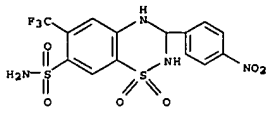
L4 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 748-19-6 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-(p-chlorophenyl)-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)



RN 3872-12-6 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(p-nitrophenyl)-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)

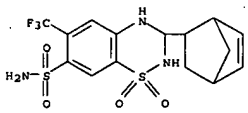


L4 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1962:423273 CAPLUS
DOCUMENT NUMBER: 57:23273
ORIGINAL REFERENCE NO.: 57:4685g-i,4686a-b
TITLE: 7-Sulfamoyl-3,4-dihydro- 1,2,4-benzothiadiazine 1,1-dioxides
INVENTOR(S): Mueller, Erich; Hasspacher, Klaus
PATENT ASSIGNEE(S): Dr. Karl Thomae G.m.b.H.
SOURCE: 4 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 1125938		19620322	DE 1960-T17869	19600212
GB 906850			GB	
PRIORITY APPLN. INFO.:			DE	19600212

GI For diagram(s), see printed CA Issue.
AB The title compds. substituted in the 3 position with a bicyclic group were
prepared by reaction of a 2,4-disulfamoylaniline with a bicyclic aldehyde or
a functional derivative thereof. Thus, 8.5 g. 6,4,1,3-Cl(H2N)C6H2(SO2NH2)2
and 4.0 g. 2,5-endomethylene-1,2,5,6-tetrahydrobenzaldehyde in 25 cc. bis(2-methoxyethyl)ether was heated 2 hrs. at 100°, the solution left at room temperature 14 hrs., 50 cc. CHCl3 added, the precipitate filtered off, and
dried to give 7.5 g. 3-(6-bicyclo[2.2.1]-2-heptenyl)-6-chloro-7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (I), m. 129-30° (aqueous MeOH). I (6.0 g.) was hydrogenated in dioxane in the presence of Raney Ni
to give 3-(6-bicyclo[2.2.1]heptyl) - 6 - chloro - 7 - sulfamoyl - 3,4 - dihydro-1,2,4-benzothiadiazine 1,1-dioxide, m. 263-6°. Treatment of 4.0 g. I with 1.6 g. Br in AcOH gave 3.0 g. 3-[6-(2,3-dibromo)bicyclo[2.2.1]heptyl] - 6 - chloro - 7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide, m. 199-201°. II prepared were (R, R1, R2, R3, R4, and m.p. given): H, 6-bicyclo[2.2.1]-2-heptenyl, H, CF3, H, 119° (AcOH-ligroine); H, 6-bicyclo[2.2.1]-2-heptenyl, Me, Cl, H, 190-1°; H, 6-bicyclo[2.2.1]-2-heptenyl, Cl, Cl, H, 184° (MeOHH2O); Me, 6-bicyclo[2.2.1]-2-heptenyl, H, Cl, Me, 232-5°; H, 6-bicyclo[2.2.1]-2-octenyl, H, Cl, H, 276-7°; H, 5-methylbicyclo[2.2.1]-2-hepten-6-yl, H, Cl, H, 197-9°. The compds. had stronger natriuretic activity than hydrochlorothiazid. Excretion of K was not increased to the same degree as that of Na.
IT 859-24-5P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)
RN 859-24-5 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-yl)-6-(trifluoromethyl)-, 1,1-dioxide (7CI, 8CI) (CA INDEX NAME)

L4 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

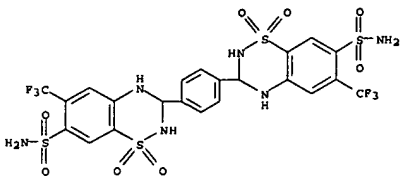


L4 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1962:7959 CAPLUS
DOCUMENT NUMBER: 56:7959
ORIGINAL REFERENCE NO.: 56:1537b-f
TITLE: Dihydrobenzothiadiazine. Diuretic activity of some new derivatives
AUTHOR(S): Selleri, Renato; Caldini, Oreste
CORPORATE SOURCE: Lab. Manetti & Roberts, Florence
SOURCE: Bollettino Chimico Farmaceutico (1961), 100, 323-9
CODEN: BCFAAI; ISSN: 0006-6648
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Cyclic derivs. of 4-amino-6-trifluoromethyl-m-benzenedisulfonamide (I) were synthesized by condensation with terephthalaldehyde (II), glyoxylic acid (III), phthalaldehydic acid (IV), pyruvaldehyde (V), phenylglyoxal (VI), and 4-biphenylylglyoxal (VII). I (6.4 g.) and 1.34 g. II in 30 cc. 1,2-dimethoxyethane with one drop concentrated H_2SO_4 were refluxed 2 hrs. and poured into 150 cc. H_2O to give, after 24 hrs., p-bis(6-trifluoromethyl-7-sulfamoyl-3,4-dihydro-1,1-dioxo-1,2,4-benzothiadiazin-3-yl)benzene, m. 300°. I (8 g.) and 8 g. III in 20 cc. H_2O with 1 drop H_2SO_4 were refluxed 0.5 hr., cooled, and dissolved in aqueous $NaHCO_3$ to give on acidification with dilute HCl 6-trifluoromethyl-7-sulfamoyl-3,4-dihydro-1,1-dioxo-1,2,4-benzothiadiazine-3-carboxylic acid (VIII), m. 238°. I (8 g.) and 3.75 g. IV in 50 cc. 1,2-dimethoxyethane with 1 drop H_2SO_4 were refluxed 2.5 hrs. and poured into 300 cc. H_2O to yield 6-trifluoromethyl-7-sulfamoyl-3,4-dihydro-1,1-dioxo-1,2,4-benzothiadiazine-(2,3:1',7')- or (3,4:1',7')benzopyrrolidinone, m. 323° (H_2O). I (11 g.) and 11 g. V in 60 cc. H_2O were refluxed for 1 hr. while adding 60 cc. 95% EtOH, then heated 1.5 hrs., and filtered. The residue was washed with EtOH and dried to give 3-acetyl-6-trifluoromethyl-7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide, m. 285-7° (EtOH). Similarly, 16 g. I and 7.38 g. VI, refluxed 2 hrs., gave the 3-benzoyl derivative, m. 340-2°, and 16 g. I and 11.6 g. VII gave the 3-(p-phenylbenzoyl) derivative, m. 241°. VIII (0.75 g.) in 5 cc. EtOH, treated with 0.558 N-diethylaminoethyltheobromine in 5 cc. EtOH, gave the salt, m. 178° (decomposition). Similarly, the VIII-N-diethylaminoethyltheophylline, m. 195-8°, VIII-piperazine, m. 215-17°, and VIII-hexamethylenetetramine, m. 187°, salts were obtained. The compds. are useful as diuretics having an action equal to or stronger than dihydrofluomethiazide.

IT 1764-14-3P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,3'-p-phenylenebis[3,4-dihydro-6-(trifluoromethyl)-, 1,1,1',1'-tetraoxide
RL: PREP (Preparation)
(preparation of)
RN 1764-14-3 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,3'-p-phenylenebis[3,4-dihydro-6-(trifluoromethyl)-, 1,1,1',1'-tetraoxide (7CI, 8CI) (CA INDEX NAME)

L4 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



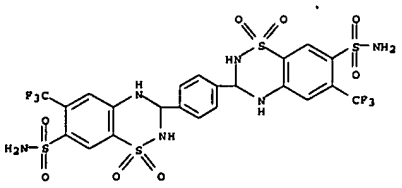
L4 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1962:7744 CAPLUS
DOCUMENT NUMBER: 56:7744
ORIGINAL REFERENCE NO.: 56:1466h-i,1467a
TITLE: Bisbenzothiadiazine derivs
INVENTOR(S): Bernstein, Jack; Yale, Harry Louis
PATENT ASSIGNEE(S): Olin Mathieson Chemical Corp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3004024		19611010	US 1959-805374	19590410
PRIORITY APPLN. INFO.:			US	19590410

AB 3,3'-Bis(1,2,4-benzothiadiazine) 1,1-dioxide compds. (I), useful as diuretics and antihypertensives, containing particularly CF_3 and sulfamoyl or N-substituted sulfamoyl groups in the benzenoid rings were prepared by condensation of a dicarbonyl, acetal, or ketal compound or a bis(dihalomethyl) derivative with a substituted o-aminobenzenesulfonamide. Thus, 31.9 g. 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide was refluxed 4 hrs. with 4.3 g. succinaldehyde in 250 ml. 95% EtOH and 25 ml. 10% aqueous HCl, the EtOH distilled, and the residue, after slowly distilling on a steam-bath with 25 ml. 20% aqueous HCl and 100 ml. EtOH, filtered to give 20 g. of an ether-washed solid. Two recrystns. from 90% aqueous MeCN gave 3,3'-ethylenebis(3,4-dihydro-6-trifluoromethyl-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide), m. 257-9° (decomposition).

IT 1764-14-3P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,3'-p-phenylenebis[3,4-dihydro-6-(trifluoromethyl)-, 1,1,1',1'-tetraoxide
RL: PREP (Preparation)
(preparation of)
RN 1764-14-3 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,3'-p-phenylenebis[3,4-dihydro-6-(trifluoromethyl)-, 1,1,1',1'-tetraoxide (7CI, 8CI) (CA INDEX NAME)

L4 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



L4 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1961:144261 CAPLUS
DOCUMENT NUMBER: 55:144261
ORIGINAL REFERENCE NO.: 55:27358f-i,27359a-i,27360a-b
TITLE: Diuretics. V. 3,4-Dihydro-1,2,4-benzothiadiazine 1,1-dioxides
AUTHOR(S): Whitehead, Calvert W.; Traverso, John J.; Sullivan, Hugh R.; Marshall, Frederick J.
CORPORATE SOURCE: Lilly Research Labs., Indianapolis, IN
SOURCE: Journal of Organic Chemistry (1961), 26, 2814-18
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 55:144261

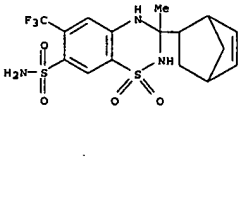
AB The synthesis and properties of 30 new 3-cycloalkenyl and 3-cycloalkyl-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1, 1-dioxides were described. Correlations between their structures and biol. activity confirmed previously proposed analogies between similarly 3-substituted 3,4-unsatd. and 3,4-dihydro derivs. of the benzothiadiazine 1,1-dioxide nucleus. The following 1-cycloalkenylacetonitriles were prepared by a known method: 1-cycloheptenylacetonitrile, 81% yield, b11 104°, n25D 1.4808; 1-cyclopentenylacetonitrile, 64%, b10 72-3°, n25D 1.4672; 3-methyl-1(or 5)-cyclopentenylacetonitrile, 80%, b10 78°, n25D 1.4488; 2-methyl-1(or 5)-cyclopentenylacetonitrile, 79%, b11 83-4°, n25D 1.4672. 1-Cycloalkenylacetonitrile (0.8 mole) in 200 ml. alc. was hydrogenated at room temperature over 2 g. 5% Pd-C with H at 50 lb./sq. in. and the cycloalkyl acetonitrile distilled 3-Methylcyclopentylacetonitrile (97% yield) b10 79°, n25D 1.4411, and cycloheptylacetonitrile (88%) b10 102°, n25D 1.4654. A solution of 0.8 mole cycloalkylacetonitrile or cycloalkenylacetonitrile in 200 ml. dioxane and 400 ml. concentrated HCl refluxed 24-48 hrs., dioxane distilled in vacuo, the organic layer extracted with Et2O and then 2% NaOH, and the basic layer acidified gave the carboxylic acid, which was distilled to yield lactones of the 1-cycloalkenylacetic acids. Cycloheptylacetic acid (57% yield) b10 146-7°, and 1-cyclohexenylacetic acid (66% yield) b13 150-5°, n25D 1.4852. 1-Cyclopentenylacetic acid and 2-oxohexahydrocyclopenta[b]furan (I) [(approx. 1:1 mixture) (II)], obtained in 41% yield, n25D 1.4771, (64 g.) treated with SOCl2 gave 25.6 g. 1-cyclopentenylacetyl chloride, b10 88-100°. I was obtained in 55% yield, b10 118-20°. 3-Methylcyclopentylacetic acid(58%) b10 120-4°, n25D 1.4472. 2-Oxooctahydrocyclohepta[b]furan (70%) b10 146-50° and 2-oxo-4(or 6a)-methylhexahydrocyclopenta[b]furan (74%) b10 111-12°, n25D 1.4636. Mg (17.2 g.), 80 ml. Et2O, 10 g. 4-norbornylenylmethyl bromide, and a crystal of iodine treated (after the reaction started) with 121.8 g. more 5-norbornylenylmethyl bromide in 250 ml., Et2O added, and the mixture refluxed 1 hr., poured into dry ice in Et2O, acidified, and extracted gave 65.5 g. 5-norbornylenylacetic acid, b12 139°, n25D 1.4878. Cycloalkyl- and cycloalkenylacetic acids were converted to the acid chlorides with SOCl2. The amides were prepared in the usual manner: the

L4 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
acid chlorides were treated with PhNHMe or NHMe2 and C5H5N in C6H6, the solns. washed with H2O, dried, and evapd. and the amides distd. in vacuo. The following RCH2CONMeR were thus obtained (R, R', % yield, b.p./ mm. given): 2-cyclopentenyl, Me, 79, 85°/0.25; 1-cyclohexenyl, Me, 75, 95°/0.4; cyclopentyl, Ph, 80, 130°/1; 1-cyclohexenyl, Ph, 80, 130°/0.3; 2-cyclohexenyl, Ph, 82, 130°/0.3; 3-cyclohexenyl, Ph, 90, 132°/0.3; cyclohexyl, Ph, 95, 136°/0.4; 3-methylcyclopentyl, Ph, 88, 104°/0.08; 5-norbornylenyl, Ph, 95, 117°/0.08; cycloheptyl, Ph, 95, 154°/1; 1-methylcyclohexyl, Ph, 98, 151°/4.5. N-Methylcycloalkyl- or N-methylcycloalkenylacetanilides (1 mole) in 220 ml. tetrahydrofuran treated in 2 hrs. with 6.25 g. LiAlH4 suspended in 150-200 ml. tetrahydrofuran, the mixt. stirred overnight and treated with dil. alc., and the product distr. gave the aldehydes. The following compds. were obtained: 2-cyclopentenylacetaldehyde, 46.5%, b12 53-6°, n25D 1.4604; cyclopentylacetaldehyde, 55%, b12 53°, b. 156°; cyclohexylacetaldehyde, 45%, b15 68-70°, n25D 1.4615; 2-cyclohexenylacetaldehyde, 33%, b13 65°; 3-cyclohexenylacetaldehyde, 27%, b10 87-127°; 3-methylcyclopentylacetaldehyde, 44%, b12 63-6°, n25D 1.4421; 1-methylcyclohexylacetaldehyde, 39%, b11 82-5°, n25D 1.4619; cycloheptylacetaldehyde, 33%, b19 98-103°, n25D 1.4652; 5-norbornylenylacetaldehyde, 32%, b8 76-8°, n25D 1.4851. The following RCH2CH:NNHCONH2 were obtained (R and m.p. given): 2-cyclopentenyl, 116-17°; 3-cyclohexenyl, 142-4°; 3-methylcyclopentyl, 126-7°; cycloheptyl, 160-1°; 1-methylcyclohexyl, 170-1°. The following 2,4-(NO2)2C6H3NHN:CHCH2R were obtained (R and m.p. given): 2-cyclopentenyl, 98-9°; cyclopentyl, 128-9°; 2-cyclohexenyl, 97°; 3-methylcyclopentyl, 91-2°; 5-norbornylenyl, 124-5°; cycloheptyl, 96-7°. Li diethoxyaluminum hydride (0.156 mole) in Et2O was added in 0.5 hr. to 0.26 mole of the N,N-dimethylcycloalkenylacetamide in 200 ml. Et2O at 0-5°, the mixt. stirred 12 hrs. at room temp. and hydrolyzed with 2N H2SO4 at 0°, and the aldehyde-Et2O soln. washed, dried, and distd. in vacuo. 2-Cyclopentenylacetaldehyde was obained in 23% yield, b12 53°, and 1-cyclohexenylacetaldehyde in 17% yield, b2.5-3.5 53-64°. 4-Amino-6-chlorobenzene-1,3-disulfonamide (28.5 g.) in 400 ml. 50% 6N HCl and alc.; 31.9 g. 4-amino-6-trifluoromethylbenzene-1,3-disulfonamide in 200 ml. 50% 6N HCl and alc.; and 33 g. 4-amino-6-bromobenzene-1,3-disulfonamide in 300 ml. warm 50% 6N HCl and alc. suspensions were prepd. The appropriate aldehyde was added to each suspension and the mixt. shaken 0.5 hr., cooled after standing 12 hrs. at room temp., the product washed, and the resultant 3,4-dihydro-3-substituted-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides were dissolved in warm alc. and dild. with H2O. The product was recrystd. from dil. alc. The following 3,4-dihydro-3-substituted-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides were obtained (3 and 6 substituents, % yield, and m.p. given): 2-cyclopentenylmethyl, Cl, 71,222°; cyclopentylmethyl, Cl, 84, 230°; cyclopentylmethyl, Br, 80, 228°; hexylmethyl, Cl, 40, 172°; 2-cyclopentenylmethyl, CF3, 70, 148°; 2-cyclohexenylmethyl, Cl, 85, 221°; 2-cyclohexenylmethyl, Br, 80, 215°; 3-cyclohexenylmethyl, Cl, 35, 215°; 3-cyclohexenylmethyl, Br, 32, 202°; cyclopentylmethyl, CF3, 70,

L4 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
156°; 1-cyclohexenylmethyl, Cl, 65, 225°; 3-methylcyclopentylmethyl, Cl, 80, 198°; 3-methylcyclopentylmethyl, Br, 80, 100°; cyclohexylmethyl, Cl, 85, 232°; cyclohexylmethyl, Br, 80, 214°; 5-norbornylenyl, Cl, 40, 210°; 2-cyclohexenylmethyl, CF3, 86, 202°; 3-methylcyclopentylmethyl, CF3, 85, 185°; cycloheptylmethyl, Cl, 93, 215°; cycloheptylmethyl, Br, 76, 214°; 1-methylcyclohexylmethyl, Cl, 35, 245°; 5-norbornylenylmethyl, CF3, 76, 228°; cycloheptylmethyl, CF3, 60, 178°; 1-methylcyclohexylmethyl, CF3, 32, 190°; 2,3-dihydro-2-(γ-pyranyl), Cl, 30, 235°; 5-norbornylenyl, Cl, 46, 234°; 2-norbornyl, Cl, 80, 263°; 6-methylcyclohexenyl, Cl, 75, 230°; 6-methylcyclohexenyl, Br, 78, 230°; 6-methyl-5-norbornylenyl, Cl, 40, 235°. 6-Chloro-3-substituted-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide (0.1 mole) in 75 ml. tetrahydrofuran was treated with 1.5 g. NaBH4, treated dropwise with 1.5 g. AlCl3 in 50 ml. tetrahydrofuran, the mixt. refluxed 2 hrs., kept overnight, and decompd., and the solids sepd. and crystd. The following results were obtained (compd., % yield, and m.p. given): 6-chloro-3-cyclopentylmethyl-3,4-dihydro-7-(N-methylsulfamoyl)-1,2,4-benzothiadiazine 1,1-dioxide, 12, 174-5°; 6-chloro-3-cyclohexylmethyl-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide, 60, -; 6-chloro-3-cyclopentylmethyl-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide, 40, -. The saluretic and diuretic activities of the compds. listed above were greater than those of the parent compd.

IT 1581-31-3P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-ylmethyl)-6-(trifluoromethyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)

RN 1581-31-3 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(5-norbornen-2-ylmethyl)-6-(trifluoromethyl)-, 1,1-dioxide (6CI, 8CI) (CA INDEX NAME)



L4 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1961:105988 CAPLUS
DOCUMENT NUMBER: 55:105988
ORIGINAL REFERENCE NO.: 55:19971b-g
TITLE: Benzothiadiazine derivatives
INVENTOR(S): Lund, Frantz; Godtfredsen, Wagn O.
PATENT ASSIGNEE(S): Lovens Kemiske Fabrik ved. A. Kongsted
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

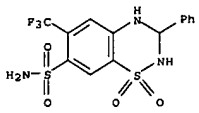
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 863474		19610322	GB	
DE 1226107			DE	
DK 97587			DK	
US 3254076		1966	US	
US 3254077		1966	US	

AB 6-Substituted 7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides (I), prepared from a substituted 2,4-disulfamoylaniline (II) and RCHO, H2C(OMe)2, or H2C:CHOR, had saluretic effects in rats and humans. Thus, a solution of 3.2 g. 5-trifluoromethyl-2,4-disulfamoylaniline, 25 ml. EtOH, and 10 ml. ethylal, and a catalytic amount of p-MeC6H4SO3H was refluxed overnight and worked up to give the 6-trifluoromethyl derivative of I, m. 271-2°. By varying RCHO (or acetal) reactant, the following 3-substituted-6-trifluoromethyl analogs of I were prepared: Me (from EtOCH: CH2, EtOCHClMe, or ClCH2CHO), m. 240-40.5°; ClCH2, m. 245-45.5;° BrCH2 (III), m. 209-10°; Et, m. 255-6°; Pr, 232-3°; iso-Pr, m. 244-5°; Bu, m.216-17°; δ-hydroxybutyl, m. 175-5.5°; n-pentyl, m. 190-1°; γ-nitropentyl, m. 243.5-5°; acetonyl, m. 208-9°; β-methoxyethyl, m. 188-90°; dicarbethoxymethyl, m. 232-4°; Ph, m. 218-19.5°; Ph2CH, m. 261-2.5°; p-methoxyphenethyl, m. 250-1.5°; benzyl (IV), m. 224-5°; phenethyl, m. 235-6°; α-phenylethyl (V), m. 243-4°; p-chlorobenzyl, 243-4°; benzyloxymethyl, m. 221-21.5°; phenoxymethyl, m. 244-6°; p-nitrophenoxymethyl, m. 261-2° (decomposition); p-aminophenoxymethyl, m. 193-4°; 2,4-dichlorophenoxymethyl, m. 230-1°; Bz, 261-2°; benzylthiomethyl, 202-3°; β-benzylthioethyl, 134-46°; 2-pyridyl, m. 304-6° (decomposition); 2-furyl, m. 190-2°; 3-cyclohexyl, m. 258-9°; 1-propenyl, m. 213-5°; n-hexyl, 178-9°; 3-pyridyl, m. 240-1°; styryl, m. 167-9°. Substitution of a ketone for the aldehyde reactant yields the corresponding 3,3-disubstituted-6-trifluoromethyl analog of I; thus, acetone and 6-trifluoromethyl derivative of II gave the 3,3-dimethyl-6-trifluoromethyl derivative of I. The following were prepared similarly: 3-methyl-3-ethyl, m. 212-13°; 3-methyl-3-chloro (VI), m. 227-7.5°; 3-methyl-3-carbethoxy, m. 191-4°; 3-methyl-3-carbethoxymethyl, m. 150-2°; cyclopentane-1,3-spiro, m. 232-4°; cyclohexane-1,3-spiro, m. 261-2°; 2-chlorocyclohexane-1,3-spiro, m. 218-19°; 4-chlorocyclohexane-1,3-spiro (VII), m. 217-18°. By varying the 5-substituent in II, the following 3,3-dimethyl-6-substituted-7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides were prepared: NO2, m. 233-3.5°; Cl (VIII), m. 230-1°; Br, m. 228-9°; MeO, m. 240-0.5°;

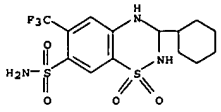
L4 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
Me, m. 243-4°; H, m. 242-2.5°. The following were prepd. similarly (substituents given): 3-Me, 3-Et, 6-Cl, m. 231-3°; 3-Me, 3-ClCH2, 6-NO2; 3-Me, 3-CO2Me, 6-NO2, m. 218-19°; cyclopentane-1,3-spiro-6-chloro, m. 234°; cyclohexane-1,3-spiro-6-bromo (IX), m. 281-3°; 2-methylcyclohexane-1,3-spiro-6-bromo, m. 231-3°; 2-chlorocyclohexane-1,3-spiro-6-chloro, m. 223-5°; 3-methyl-3-acetyl-6-chloro, m. 246-7°. Tests on groups of ten persons indicated that 2.0 mg. IV had the same saluretic effect as 20 mg. of the 6-Cl deriv. of I. III-IX were potent saluretic agents in rates.

IT 1170-25-8P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide 4454-81-3P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-cyclohexyl-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)

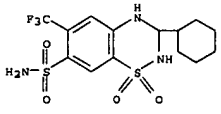
RN 1170-25-8 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide (6CI, 7CI, 8CI) (CA INDEX NAME)



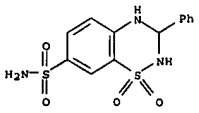
RN 4454-81-3 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-cyclohexyl-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide (6CI, 8CI) (CA INDEX NAME)



L4 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 100395-18-4 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-, 1,1-dioxide (6CI) (CA INDEX NAME)

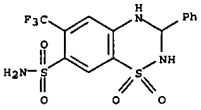


L4 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1961:39254 CAPLUS
DOCUMENT NUMBER: 55:39254
ORIGINAL REFERENCE NO.: 55:7664d-f
TITLE: Aromatic sulfamoyl compounds with diuretic action
AUTHOR(S): Lund, P. J.; Kobinger, W.
CORPORATE SOURCE: Research Labs. Leo Pharm. Prods., Copenhagen
SOURCE: Acta Pharmacologica et Toxicologica (1960), 16, 297-324
CODEN: APTOA6; ISSN: 0001-6683
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A relation was found between constitution and activity of substituted 2,4-disulfamoylanilines (DSA) and substituted 7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides (DBT). DSA and DBT compds. showed a distinct relation between substitution in the benzene ring and saluretic activity. Substitution in the heterocyclic ring of DBT compds. yielded some substances considerably more potent than the known hydroflumethiazide (6-trifluoromethyl-7-sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide) and hydrochlorothiazide. Of these substances, benzylhydroflumethiazide (Centyl) (the 3-benzyl derivative of hydroflumethiazide), which in human expts. showed the saluretic activity expected on the basis of the animal expts., was selected for further clin. use. Among the active substances studied, no differences in the urinary electrolyte-excretion pattern were detected by the method used.

IT 1170-25-8, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide 4454-81-3, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-cyclohexyl-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide 100395-18-4, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-, 1,1-dioxide
(as diuretic)

RN 1170-25-8 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide (6CI, 7CI, 8CI) (CA INDEX NAME)



RN 4454-81-3 CAPLUS
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-cyclohexyl-3,4-dihydro-6-(trifluoromethyl)-, 1,1-dioxide (6CI, 8CI) (CA INDEX NAME)

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ACCESSION NUMBER: 1960:11460 CAPLUS
DOCUMENT NUMBER: 54:11460
ORIGINAL REFERENCE NO.: 54:2351f-i,2352a-f
TITLE: Synthesis of trifluoromethylated compounds possessing diuretic activity
AUTHOR(S): Holdrege, Charles T.; Babel, Richard B.; Cheney, Lee C.
CORPORATE SOURCE: Bristol Labs., Inc., Syracuse, NY
SOURCE: Journal of the American Chemical Society (1959), 81, 4807-10
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 54:11460

AB Hydrated Na2S (113.5 g.) (containing 61% Na2S), 28.4 g. S, and 500 cc. H2O warmed on the steam bath to solution, the solution added dropwise with stirring to 400 g. 4,3-Cl(O2N)C6H3CF3 in 1.5 l. refluxing MeOH, refluxed 1 hr., cooled, and filtered yielded 359 g. [4,2-CF3(O2N)C6H3S]2 (I), m. 158-61° (AcOH). I (1000 g.) in 2.3 l. glacial AcOH and 250 cc. H2O treated 4 hrs. at 5-14° with gaseous Cl, heated 2 hrs. at 70°, cooled to 10°, chlorinated again 7 hrs., kept overnight, heated 0.5 hr. on the steam bath, and poured into 6 l. ice and H2O, the aqueous phase extracted with 1 l. PhMe, and the combined organic phase and extract evaporated gave crude 4,2-CF3(O2N)C6H3SO2Cl (II). The crude II added during 3 hrs. to 2 l. cold concentrated NH4OH below 15°, kept overnight, and filtered, the residue slurried with 4 l. 10% aqueous NaOH at 15°, filtered, acidified below 25°, cooled, and filtered, and the residue recrystd. from 2 l. iso-PrOH gave 490 g. 4,2-CF3(O2N)C6H3SO2NH2 (III), m. 165-7°; 2nd crop 66 g. A similar run with double the chlorination time yielded 54% III. III (5 g.) and 5 cc. glacial AcOH in 150 cc. H2O heated on the steam bath while being treated with 6 g. Fe filings in 2 portions 5 min. apart, stirred 3 hrs. on the steam bath, diluted with 100 cc. 95% EtOH, heated to boiling, filtered, neutralized hot with saturated aqueous Na2CO3, filtered, and cooled gave 3 g. 2-NH2 analog (IV) of III, m. 143-6° (aqueous EtOH). Fe filings (242 g.) added in portions during 1.5 hrs. to 242 g. NH4Cl, 190 g. III, 2 l. MeOH, and 1 l. H2O, the mixture refluxed 1.5 hrs., and filtered hot, the cake washed with 400 cc. MeOH, the combined filtrates diluted with 4.5 l. H2O, heated to boiling, filtered, and cooled to 0°, and the precipitate recrystd. from a mixture of 400 cc. H2O and 250 cc. MeOH containing 2 cc. 6N HCl yielded 126 g. IV, m. 141-5°. IV (35 g.) added during 0.5 hr. to 96 cc. ClSO3H with stirring and cooling, the mixture treated without cooling during 1 hr. with 87.6 g. NaCl, heated rapidly in a bath from 85 to 150°, kept 15 min. at 150°, and poured into 600 g. ice and H2O precipitated gummy 4,6,1,3-H2N(F3C)C6H2(SO2Cl)2 (V). The crude V added to 200 cc. concentrated NH4OH, kept overnight, heated on the steam bath, and cooled gave 15.7 g. 4,6,1,3-H2N(F3C)C6H2(SO2NH2)2 (VI), m. 239.5-41.5° (H2O). VI (1 g.) and 4 cc. 98% HCO2H refluxed 4 hrs., cooled, and filtered gave 7-sulfamoyl-6-trifluoromethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide

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m. 300-2° (cor.) (1:1 95% EtOH-H2O). IV (45 g.) chlorosulfonated in the usual manner, 1/2 of the resulting V extd. with 125 cc. dioxane, the ext. treated with 15 cc. 40% aq. CH2O, kept at 10° overnight, basified with 125 cc. concd. NH4OH, kept 1.5 hrs. at room temp., heated 1 hr. on the steam bath, refluxed 2.5 hrs., cooled with ice, and filtered yielded 0.6 g. 3,4-dihydro deriv. (VIII) of VII, m. 260-4° (aq. EtOH). VI (63.8 g.), 16.5 g. 40% aq. CH2O, 300 cc. H2O, and 0.1 cc. concd. H2SO4 refluxed 3.5 hrs. with stirring, cooled, and filtered, and the residue recrystd. with 1.5 g. C from 400 cc. MeOH and 200 cc. H2O gave 43.5 g. VIII, m. 262-5°, 271-4° (cor.). Crude V from 22 g. IV added to 250 cc. 40% aq. MeNH2, kept overnight at room temp., and filtered, the filtrate concd., cooled, and filtered, and the residue dissolved in the min. amt. of MeOH at room temp. and repptd. with an equal vol. of H2O gave 11 g. 4,6,1,3-H2N(F3C)C6H2(SO2NHMe)2, m. 168-70° (H2O). VI (5 g.) and 45 cc. Me2C(OMe)2 refluxed 24 hrs. and evapd. gave 1.6 g. 3,3-di-Me deriv. of VII, m. 216-21° (aq. MeOH). VI (5 g.), 0.0173 mole appropriate aldehyde, 1 drop concd. H2SO4, and 30 cc. H2O refluxed, cooled, and filtered, and the residue recrystd. from Et2O aq. MeOH or aq. Me2CO gave the corresponding 3-substituted VII (IX); method A. VI (5 g.), 0.0173 mole appropriate aldehyde, and 30 cc. glacial AcOH refluxed and evapd. in vacuo, and the residue recrystd. from aq. MeOH gave the corresponding IX; method B. VI (5 g.), 0.0173 mole ethylene ketal of an appropriate cycloalkanone, 2 drops concd. H2SO4, and 50 cc. BuOH refluxed and evapd. in vacuo, and the residue recrystd. from aq. MeOH yielded the corresponding IX; method C. By these methods were prepd. the following IX (3-substituent, m.p., method, reactant, % yield, and reflux time given): Et, 262-3° (decompn.), A, EtCHO, 59, 4; Me, 247-50° (decompn.), A, AcH, 70, 0.25; PhCH2, 221-3°, B, PhCH2CHO, 35, 16; 2-pyridyl, 310-11°, A (without the H2SO4 catalyst), 2-C5H4NCHO, 19, 0.5; CCl3, 283-5° (decompn.), A, CCl3CH(OH)2, 22, 24; Ph, 220-4°, B, BzH, 17, 24; pentamethylene, 260-2°, C, cyclohexanone ethylene ketal, 23, 1.5; tetramethylene, 225-6° (decompn.), C, cyclopentanone ethylene ketal, 19, 2. VI and VII were potent orally active diuretics of low toxicity; VII was about 10 times as active orally as VI in animals.

IT 1170-25-8P, 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide
RL: PREP (Preparation)
(preparation of)

RN 1170-25-8 CAPLUS

CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-phenyl-6-(trifluoromethyl)-, 1,1-dioxide (6CI, 7CI, 8CI) (CA INDEX NAME)

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